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PATENT

Rev 06/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application	:	Andrew W. Taylor et al.
Application No.	:	09/912,670
Filed	:	July 23, 2001
Confirmation No.	:	6394
For	:	ACTIVATION OF REGULATORY T CELLS BY ALPHA-MELANOCYTE STIMULATING HORMONE
Examiner	:	Gerald R. Ewoldt
Attorney's Docket	:	ERIZY-114AX

TC Art Unit: 1644

* *

I hereby certify that this correspondence is being sent via facsimile to Examiner Gerald R. Ewoldt, TC Art Unit 1644, Fax No. (571) 273-8300, on July 28, 2005.

By: Holliday C. Heine
Holliday C. Heine, Ph.D.
Registration No. 34,346
Attorney for Applicant(s)

* *

DECLARATION OF DR. ANDREW W. TAYLOR UNDER 37 C.F.R. §1.132

Via Facsimile
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Andrew W. Taylor, a citizen of the United States, residing at 34 Weir Road, Waltham, Massachusetts 02451, declare the following:

1. I hold a Ph.D. in Microbiology and Immunology from The Ohio State University, Columbus, Ohio. I also carried out post-doctoral research at the Department of Immunology and the Department of Ophthalmology at the University of Miami School of Medicine, Miami, Florida. At the present time, I hold the position of Associate Scientist at The Schepens Eye Research Institute, Inc., located in Boston, Massachusetts.

2. My expertise and experience are in the areas of Immunology, Neuroimmunology, and Biochemistry. I have published numerous articles relating to Immunology, Neuroimmunology, and Biochemistry, such as: Taylor AW. Neuroimmunomodulation in immune privilege: role of neuropeptides in ocular immunosuppression (Revised). Neuroimmunomodulation. 2002, 10:189-198. (PMID: 12584406); Taylor AW. A mini-review of the influence of aqueous humor on immunity. Ocul Immunol Inflamm 2003; 11:231 - 241. (PMID: 14704895); Kitaichi N, Namba K, and Taylor AW. Inducible immune regulation following autoimmune disease in the immune privileged eye. J. Leuk. Biol. 2005; 77:496-502. (PMID: 15647326); Taylor AW. The immunomodulating neuropeptide alpha-melanocyte stimulating hormone (alpha-MSH) suppresses LPS-stimulated TLR4 with IRAK-M in macrophages. J. Neuroimmunol. 2005; 162: 43-50. (PMID: 15833358).

3. I am an inventor of the subject matter described and claimed in the above-identified patent application. I am also familiar with the prosecution of the present application before the United States Patent and Trademark Office.

4. In the final Office Action, the Examiner again rejected the pending claims as obvious over US Patent No. 6,048,850 in view of Lipton et al. (alone or in combination with Singh et al.).

5. The Applicants subsequently (May 11, 2005) filed a Request for Continued Examination (RCE) and Preliminary Amendment. In the Preliminary Amendment, independent claim 24 was amended to read as follows:

> 24. (Currently Amended) A method for down-regulating a T cell-mediated autoimmune response in an affected tissue site in an animal, comprising locally injecting genetic material for expressing α-MSH, into or near the autoimmune-diseased tissue site.

The Applicants stated as follows in the Preliminary Amendment:

> Applicants submit that Lipton discloses at most only generalized systemic treatment of acute inflammation using α-MSH and in no way teaches or hints at the method of the invention as particularly claimed in amended claim 24. Therefore, Lipton can add nothing to the disclosure of the '850 patent, which generally teaches gene therapy for treating inflammation. Thus, Applicants submit that the rejection of claims 24 and 43 has been overcome.

6. Since the filing of the RCE, I have carried out certain experiments testing the method of the invention as particularly claimed. Specifically, I have tested the difference between injecting the genetic material into the eye (local treatment) versus injecting the genetic treatment into the peritoneal cavity (systemic treatment) on the severity and duration of experimental

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autoimmune uveoretinitis (EAU). Referring to Figure 1 and Figure 2 in the accompanying Appendix, one can see that only a localized injection of genetic material coding for alpha-MSH as particularly claimed, and therefore a localized production of alpha-MSH in the eye, was effective in suppressing the severity and duration of autoimmune disease in the eye.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code, and that such willful false statements so made may jeopardize the validity of the document, or application, or any patent issuing thereon.

Date July 20, 2005

By Andrew W. Taylor
Dr. Andrew W. Taylor

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Figure 1. The effects of α-MSH plasmid delivery on the course of experimental autoimmune disease.

Methods. The B10.RIII mice were immunized to induce EAU by standard methods. On days 6 and 9 after the immunization, the mice were injected with 5μg α-MSH-encoded plasmid (source: ZYCOS) into the eye (local injection) or in the peritoneal cavity (IP, systemic injection). The control mice were injected with 5μg of empty plasmid (Source: ZYCOS) into the eye. The mice eyes were examined every three days and scored on a scale of 0-5 with 0 for no inflammation and 5 for severe inflammation with retinal detachment and hemorrhage.

Results. Only the mice that were injected with α-MSH-encoded plasmid into the eye had a significant suppression in the inflammation and duration of EAU compared to the mice injected with the empty plasmid and with the mice systemically injected with α-MSH-encoded plasmids. The average EAU score of the mice injected with α-MSH-encoded plasmid into the eye remained below a score of 1. This indicates that there is very little if any inflammation in these eyes unlike the other two groups. *These daily average scores are significantly different ($P \leq 0.05$) from the corresponding daily average score of the mice receiving an injection of empty plasmid. Significance was calculated using Mann-Whitney non-parametric analysis. In addition, there was no statistical difference between the systemic injection of α-MSH-encoded plasmid and the eye injection of empty plasmid; whereas, there was a significant difference between the eye injected and systemic injection of α-MSH-encoding plasmid.

Conclusion. Only a localized injection of α-MSH-plasmids, and therefore a localized production of α-MSH in the eye was effective in suppressing the severity and duration of autoimmune disease in the eye.

Appendix to Declaration of
Andrew W. Taylor

Figure 2. The effects of α-MSH plasmid delivery on the maximum EAU scores.

Methods. From the data generated above in Fig. 1, we recorded for each mouse their highest EAU score of either eye during the course of EAU. This maximum EAU score is represented as a single symbol on the graph separated by their respective groups. The horizontal line marks the average maximum score of the groups.

Results. There is a statistically *significant ($P \leq 0.05$) suppression in the maximum scores of the mice injected into their eyes with α-MSH-encoded plasmid compared to both groups of mice injected with empty plasmid or systemically injected (IP) with the α-MSH-encoded plasmid. There was no statistical difference between the group of mice injected with empty plasmid and the group of mice systemically injected (IP) with the α-MSH-encoded plasmid.

Conclusion. Only a localized injection of α-MSH-plasmids, an therefore a localized production of α-MSH in the eye was effective in suppressing the severity of autoimmune disease in the eye.

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